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Dose-volume correlates of mandibular osteoradionecrosis in oropharynx cancer patients receiving intensity-modulated radiotherapy: Results from a case-matched comparison

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Abstract

Purpose—To determine dosimetric parameters associated with Osteoradionecrosis (ORN) in oropharyngeal cancer (OPC) patients in the IMRT era.

Material and Methods—Subsequent to institutional review board approval, we identified ORN in OPC patients treated with IMRT from 2002–2013. 1:2 case-control matching was implemented. Mandibular dose-volume histograms (DVH) were extracted. Dosimetric parameters were compared using non-parametric stats. Recursive partitioning analysis (RPA) was done to identify DVH correlates of ORN.

Results—68 ORN cases and 131 controls were matched. Median follow-up was 41 months and median time to development of ORN was 16 months. Mandibular mean dose was significantly higher in the ORN cohort (48.1 vs 43.6 Gy, $p < 0.0001$). However, the maximum dose was not statistically different. DVH bins from V35 to V73 were all significantly higher in the ORN cohort

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compared with controls ($p < 0.0006$). Two DVH parameters were identified in RPA analysis, V43 and V58. The majority (81%) of ORN cases were observed with both V44≥42% and V58≥25%.

Conclusions—Our data demonstrate that a wide range of DVH parameters in the intermediate and high beam path were all significantly higher in ORN patients. Mandibular V44<42% and V58<25% represent reasonable DVH constraints for IMRT plan acceptability, when tumor coverage is not compromised.

Keywords

Osteoradionecrosis; Oropharynx cancer; Head and Neck cancer; Dose-volume histogram; Mandible; Intensity-modulated radiotherapy

Introduction

Osteoradionecrosis (ORN) is a highly morbid sequel of radiotherapy. The advent of intensity modulated radiotherapy (IMRT), and the ability to limit dose to adjacent non-target structures improves the technical capacity to limit dose to at risk mandibular bone. As such, development of ORN in the IMRT era should become an increasingly rare phenomenon. However, there remains debate regarding the true incidence of ORN in the modern era, as retrospective studies of ORN development over the last 2 decades paint a mixed picture. A recent SEER-Medicare analysis of oral cancer patients, demonstrated a non-significant trend of lower rate of jaw complications after IMRT (14%) compared with non-IMRT (17%)[1], while some single institution reports purport no[2] or less than 1%[3] rate of ORN with use of aggressive dental care and IMRT. A recent study, however, reported no reduction in ORN rates in oropharyngeal cancer patients after IMRT in comparison to conventional 3D conformal radiotherapy techniques.[4] Most single-institution series of oral/oropharyngeal cancer patients treated with radiotherapy demonstrate frank osteoradionecrosis rates of approximately 1–11% [5–10]. Consequently, as Thariat et al.[11] assert, “this low incidence may indeed make the establishment of statistically relevant correlations between dose and ORN difficult.”

Despite the enthusiasm of some to declare ORN a historical consideration, a careful review of IMRT beam path reportage suggests that, in addition to maximum point doses approximating those of 3-DCRT patients, a significantly larger part of the anterior mandible may be subjected to a “beam path” toxicity unobserved in previous eras. [12] Consequently, given the mandibular volume receiving low- or intermediate- dose, it remains unclear what dose-volume parameters are best used as constraint(s) to minimize the risk of ORN. Several groups have reported different dose correlates and various permutations of maximum and mean mandibular dose as usable constraints[6, 7, 13, 14]. Traditionally, doses under 50 Gy were considered unlikely to contribute substantively to osteoradionecrosis, and most recommendations and clinical protocols restrict dose only above 50 Gy or more[5–10].

As part of an ongoing programmatic effort to investigate beam-path toxicities in head and neck cancer, we sought to ascertain the optimum dose constraints for institutional utilization, as well as to provide a risk assessment threshold for previously treated patients.

The specific aims of the current study include:

- Characterization of ORN beam path dose-response kinetics in a series of patients with prophylactic dental management treated with IMRT in the modern era.
- Identification of specific candidate dose-volume parameters associated with increased probability of ORN.
- Determine testable hypotheses for future prospective research efforts.

Methods

Patient selection

Subsequent to Institutional Review Board approval, we used automated data extraction to identify ORN event in head and neck cancer patients treated with IMRT from 2002–2013. This was accomplished by querying all radiology reports from the Radiology Information Systems (RIS), filtering for CT scans of the head and neck containing one of the following terms: “osteoradionecrosis”, “ORN”, “exposed bone”, “hyperbaric oxygen”, “exposed mandible”, “osteonecrosis”, and “radionecrosis”. Patients with reports meeting the above criteria were further filtered for ones with clinical notes from the Radiation Oncology service in the electronic medical record. Flagged records were then manually screened for secondary inclusion. The following inclusion criteria were applied for ORN patient selection for this analysis: confirmed pathological diagnosis of oropharyngeal squamous cell carcinoma, treatment using IMRT, no prior recorded head and neck irradiation, and documented diagnosis of mandibular ORN following IMRT.

Available archival dose volume histogram (DVH) data for the mandible were subsequently extracted to a research database using commercial treatment planning software (Pinnacle 9.4, Phillips Medical Systems, Andover, MA). One-to-two case control matching was then implemented for ORN cases with patients extracted from a well-curated extant institutional head and neck surgery/speech pathology oral toxicity and functional outcome database of oropharyngeal cancer patients treated by IMRT during the same period [15]. Inclusion criteria for controls were: 1) incident cases of oropharyngeal squamous cell carcinoma, 2) treated at MDACC between 2002–2013 with curative-intent IMRT, 3) minimum of 1 year disease-free follow-up, and 4) no documentation of ORN or related sequelae (e.g. soft tissue necrosis or osteomyelitis).

Case-control matching was based on the following variables: age (within 5 years), sex (same sex), ethnicity (within 1 category difference), smoking status (same smoking status), and T stage (within 1 stage difference). For each case, up to 2 matched controls, meeting matching criteria, were selected by optimal matching algorithm, utilizing SAS macro, %match. Optimal matching produces the matched controls with the smallest total distance between cases and matched controls[16]. The original delivered DICOM-RT clinical treatment plans for controls were also imported into the research database to extract mandibular DVH of the control cohort.

Dental evaluation

Dental oncology documentation were reviewed for pre- and post-IMRT dental status and all dental procedures were recorded. All patients received pre-radiotherapy Dental Oncology service clearance, and, if indicated, prophylactic dental extraction and fluoride trays, were received as per standard Head and Neck Service operating procedure.

IMRT

The details of our institutional IMRT approach for oropharyngeal cancer patients were previously reported in detail [17]. Briefly, IMRT was used to treat the primary tumor and upper neck nodal disease by a split-field technique matching with a lower anterior neck field with a larynx midline block. While “whole-field” IMRT was used only when tumors were located at the junction to avoid under-dosing. In general, 66 Gy was prescribed to treat small volume primary tumors and 70–72 Gy for more advanced tumors. Patients were planned using the Pinnacle planning system (Philips Medical Systems, Andover, MA) and IMRT was delivered using Varian 6-MV photons linear accelerators (Varian Medical Systems, Palo Alto, CA).

ORN grading

The ORN was graded as follows: grade I: minimal bone exposure requiring conservative management; grade II: minor debridement received; grade III: hyperbaric oxygen needed; grade IV: major surgery required.[7]

Follow-Up

The first post-radiation follow-up was at 8 to 12 weeks after treatment completion, subsequently every 2 to 3 months for the first year, every 3 to 4 months for the second year, and at least once a year thereafter. Detailed clinical examination of the oral cavity is performed as part of routine oncologic follow up at every visit and surveillance imaging is reviewed by a dedicated head and neck radiologist with experience in radiation associated sequelae such as ORN. Whenever clinical exam or imaging was suspicious for interim ORN development, dedicated evaluation by dental oncology was obtained.

Statistical analysis

Comparison of individual dose-volume bins from 1 Gy up to 75 Gy (V1–V75), mean, and maximum mandibular dose between ORN and non-ORN matched cohorts were assessed by non-parametric analysis with the Wilcoxon rank-sum test. Patient dose distributions were initially interrogated via bivariate plots of cumulative group binned DVHs, dichotomized by the presence or absence of ORN. For multiple comparison of the significance of each dose-volume bin from V1–V75, a Bonferroni correction was performed with $\alpha < 0.0006$ (i.e. accounting for n=75 bins) deemed significant.

Recursive partitioning analysis (RPA)[18, 19] was utilized to evaluate the extent to which patients with ORN could be identified from dosimetric parameters using a clinically applicable strategy based on iterative thresholding. The technique explores all possible combinations of thresholds among a candidate set of parameters through an iterative, two-

stage process. Decision trees are formulated through a recursive splitting process that selects the next best variable and its optimal partition. The splitting process concludes after no further improvements are possible, after which cross-validation is applied to identify the optimal decision tree for prediction based on minimal estimate risk (or misclassification loss). Using the presence of ORN as the binary class variable, tree-based thresholds were identified from predictors derived from extracted DVH data in 1 Gy bins. DVH data was converted to a range of continuous volumetric parameters (V1–V75) representing the volume receiving a given dose or more (e.g., a V50 of 10% denotes that 10% of the specified patient's mandible received ≥50 Gy). Patients were assigned to a training and validation subsets (80:20) at random as a "pre-processing" step. To define a specific dose-volume thresholds within candidate parameters, a decision tree-based partitioning was performed and a minimum split size of 10% per split/partition. An *a priori* $\alpha = 0.05$ was specified for significance, with iterative trees splits adjusted using a Bonferroni-corrected logworth (i.e. the negative log of the p-value), with subsequent pruning after the first split demonstrating non-significance[18]. While readily clinically interpretable and robust against distributional assumptions, this approach suffers from the limitation that each 1-Gy bin is considered independently, while in reality, for photon plans, dose-volumes are necessarily inclusive of the cumulative integral dose of lower dose-volume bins (e.g. a patient cannot logically have a V50 of 55% and a V40 of <55%).

To account for this limitation and utilize more of the acquired information, we implemented a multivariate approach based on Bayesian quadratic discriminant analysis [20, 21] (BQDA) to evaluate the extent to which DVH characteristics could be integrated via continuous multivariate analysis to discriminate ORN from non-ORN on the basis of characteristics of the mandibular dose-volume. The Bayesian multivariate approach estimates the mean and covariance for the set of predictors for each class (ORN versus non-ORN) and yields a posterior probability measuring the extent of evidence that an inter-feature distribution arises from each candidate class[20, 21]. Receiver-operating-characteristics (ROC) curves were evaluated with respect to the resultant posterior probabilities. A final model was selected to yield the highest area under the ROC curve (AUC) based on the training data (a random subset comprising 80% of patients) for integration of up to five DVH discrete parameters. Delong's 95% confidence interval (CI) [22] was reported for Bayesian classifiers resulting from both training and validation sets. Combing training and validation sets, ROC performance was also measured under leave-one-patient out cross-validation. Parameters for each class assumed independent priors, and inter-class mean vectors assume flat priors. The prior probability of each was assumed to be 0.5. An unstructured covariance was estimated for each class, which assumed an inverse Wishart prior with shape=number predictors and scale matrix estimated from the data as the maximizer of the marginal density (empirical Bayesian method). Derivation of the Bayesian classifier is provided in the supplementary technical appendix. The sample size of 199 patients provides 80% power to detect an AUC of at least 0.62 at α=0.05 assuming 68 cases of ORN.

RPA was implemented using statistical software R version 3.2.3 (R Development Core Team, http://www.r-project.org) [23] with the rpart package[24] with split selection criteria based on the Gini Index, equal cost between false negative and false positive results, and prior class probabilities specified as the sample proportions. BQDA was carried out using

statistical software R version 3.2.3 using the analysis scripts published in Wang et al.[20]. All other statistical analysis was performed using commercial statistical analysis software (JMP v11Pro, SAS Institute, Cary, NC, USA).

Results

Patients

A total of 83 patients with documented ORN diagnosis met the inclusion criteria. Of those 72 had available DVH data. Four hundred forty potentially eligible controls were identified by query of an institutional head and neck cancer registry. A total of 440 patient charts were reviewed. One hundred sixty-seven patients were excluded per the following criteria: death or lost to follow-up before 1 year (n=38), radiation therapy at an outside facility (n=11), less than 1 year of disease-free follow-up (n=20), history of ablative head and neck surgery in study period (n=3), insufficient treatment details (n=10), delayed neck dissection for regional recurrence (n=4), preoperative neck dissection (n=1), ORN diagnosis (n=12), no available IMRT plan archived (n=66), and corrupt DVH data (n=2). The remaining 273 with available DVH data were included. For each ORN case up to 2 controls were selected (if matched controls were available). Eventually, 68 ORN cases and 131 controls were selected (2 controls each for 63 cases and 1 control each for 5 cases). Demographic, disease, and treatment characteristics of the matched case-control patients are summarized in Table 1.

Median follow-up time for all patients was 61 months (range 13–133); median time to development of ORN was 16 months from completion of radiotherapy (range 2–118). The distribution of ORN grades was as follows: grade I (n=15, 22%); grade II (n=18, 26.5%); grade III (n=16, 26.5%); and grade IV (n=17, 25%).

Dosimetric comparison

The mandibular mean dose (Dmean) in the ORN cohort was significantly higher compared with controls by non-parametric analysis as a continuous variable (48.1±7.1 vs 43.6±6.4 Gy, $p < 0.0001$). However, the maximum dose (Dmax) was not statistically different in both cohorts; 74.0±2.5 Gy in ORN cohort compared to 73.2±3.9 Gy in controls ($p = 0.06$)

Grouped dose-volume histogram information for cases demonstrating ORN and controls is shown in Figure 1; notably, percent volumes for all 1-Gy dose bins between 25 Gy and 74 Gy yielded p-values <0.05, though no dose-levels below nor above were distinct. After Bonferroni correction, DVH bins from V35 to V73 were all significantly higher in the ORN cohort compared to controls with $p < 0.0006$ as shown in Figure 1. This suggests that DVH differences are attributable to beam path “bath” dose in the intermediate to high dose range (35–73 Gy), as opposed to low dose (<35 Gy) or doses higher than 73 Gy.

For the ORN only cohort, a similar comparison was done for all DVH bins between patients with low grade I-II (n=35) and higher grade III-IV (n=33) ORN. This revealed no statistically significant difference across all bins as shown in Figure 2.

RPA using a decision-tree based approach was implemented for all candidates. Two DVH parameter splits were identified as meeting the pre-specified statistical significance criteria

in the training dataset (n=154): V43 at the initial node and V58 at the second node. Within the training dataset, 0/27 (0%) patients with a V43<42% had ORN, 9/43 (21%) patients with V44≥42% and V58<25% had ORN, while 41/84 (49%) patients with both V44≥42% and V58≥25% had ORN. In the validation dataset, 2/14 (14%) patients with a V43<42% had ORN, 2/6 (33%) patients with V44≥42% and V58<25% had ORN, while 14/25 (56%) patients with both V44≥42% and V58≥25% had ORN. Figure 3 shows a bar chart of ORN rate in the entire dataset by various V43 and V58 combinations, wherein the majority (81%) of ORN cases were observed with both V44≥42% and V58≥25%.

BQDA identified five dose-volume parameters as discriminatory of ORN when combined in multivariate analysis; V45, V49, V61, V65, and V72. The resultant model yielded ROC AUCs of 0.81 (95% CI 0.74–0.88) and 0.87 (95% CI 0.76–0.98) for the training and the validation set, respectively, when using the resultant probability measures for classification (Figure 4). Combing training and validation sets, ROC performance measured under leave-one-patient out cross-validation resulted in AUC of 0.75 (95% CI= 0.68–0.82). Table 2 shows model estimated means of the resultant parameters between ORN and non-ORN cohorts, while supplementary figure 1 shows the estimated correlation matrices. Both describe the elliptical surface that best separates the two cohorts.

Discussion

ORN, long a scourge of head and neck cancer survivorship, has, by most reports, been substantively reduced in the modern radiotherapy era by use of IMRT for mandibular dose reduction and careful dental management; and to some, there is a suggestion that ORN may represent a “historical” toxicity[2, 25]. Nonetheless, we have previously noted that beam path assessment of non-target organs showed no appreciable difference in median hottest voxel in the posterior mandible, and actually demonstrated a *several-fold increase* in the anterior and mid-mandibular dose[12]. In the current study we identified 83 patients with post-IMRT ORN in oropharyngeal cancer patients. Given that ~1700 patients were treated with IMRT for oropharyngeal cancer during the study inclusion period, we estimate an institutional incidence rate of approximately 5%. This rate approximates a previous retrospective institutional survey by Tsai et al[7], who showed out of 402 surveyed charts, a 7.5% ORN rate, in a mixed IMRT/3D-CRT cohort, but well below the observed 16% jaw complication rate (including ORN) shown by Beadle et al.[1] in a population-wide large-scale national registry dataset. However, the identification of the true incidence of ORN in the current series is limited by the lack of detailed dental care data for some patients who opt to follow-up at different facilities close to their home residence, the opacity in diagnostic criterion for ORN, and the limitations of our data extraction/data query parameters that represent a limitation of any retrospective series.

Using matched pair analysis in a previous smaller dataset, it was observed that V50 and V60 differences were comparatively different between ORN patients and matched controls [7]. The current dataset consists of only IMRT treated patients, thus representing a robust sample for the undertaken analyses. To our knowledge, this study presents the largest oropharyngeal ORN series in the IMRT era. Our data demonstrate, in a well-matched ORN case-control

cohort, that a wide range of DVH parameters ranging from V35 to V73 were all significantly higher in the ORN patients compared to asymptomatic controls, as shown in Figure 1.

Several mechanistic models for ORN development are currently utilized. Marx et al.[26–28] posit a model whereby microvascular depletion and alteration due to radiotherapy leads to hypoperfusion, hypoxia, and metabolic insufficiency, while Delanian and Lefaix suggest profibrotic alterations in bone represent the dominant pathophysiologic process[29–31]. Animal studies have demonstrated dose-dependent osteogenic cell depletion and biomechanical impairment; however, most animal studies use abbreviated schedules, or fractional doses larger than those typically received in IMRT plans.

The current dataset confirms that maximum dose to the mandible *as a single dose constraint* is a comparatively poor correlate with ORN, and should thus likely be eschewed without additional volumetric limits to the mandible OAR ROI. Our findings are also consistent with reports from other investigators. Gomez et al., in a similar analysis [6], showed the Dmean >40Gy was associated with increased risk of ORN in patients receiving dental extractions; a *post hoc* analysis of Dmean >40 Gy as a binary variable in our data set showed it was significantly associated with ORN (Chi-square p=0.001), confirming that intermediate dose level (~40 seen in their study are retained in our dataset.

Furthermore, it appears that all doses in the intermediate and high range (Figure 1) are more likely to be elevated in ORN patients. We also observed that V43 and V58 are comparatively more distinct between ORN and non-ORN patients using an RPA-derived decision tree. These findings hew closely to previous work by Tsai, which matched dosimetric data from 25 ORN patients and 40 controls to show V40–V60 as being elevated in matched-pair analysis[7]. These findings serve to reiterate the value of reducing DVH parameters as low as V35 whenever possible relative to the location of tumor and nodal volumes. Thus, constraints for treatment planning of mandibular ORNs should likely utilize several volumetric constraints, rather than a single point-dose maximum.

Regarding identification of specific parameter dose-volume constraints, our data suggest that V44≥42% and V58≥25% provide a comparatively robust association with ORN development as shown in Figure 3. Additionally, our probabilistic-based Bayesian multivariate approach, which identified the “optimal” combination of DVH parameters for discriminating between ORN cohorts in multivariate analysis, yielded ROC AUC of 0.81 and 0.87 when classifiers ranging from V45–V72 were utilized to discriminate ORN in the training and validation set, respectively. This represents a paradigm shift from evaluations based on single individual parameters and application of cut-off thresholds. While this is an institution-specific finding, it points again to the fact that beam path doses substantively under the prescription dose may be deleterious to mandibular osteocytes, and suggest that intermediate “bath” (e.g. ranging from >35–45 Gy) should likely be constrained when possible as well, rather than focusing only on high (>60Gy) dose regions as a criterion for plan acceptance.

While confirmatory data are required for generalization, other sources of uncertainty may remain unaccounted for; as with any single-site retrospective analysis, the standard caveats

apply. However, these data represent a reasonable institutional benchmark, and are being used internally for prospective ORN assessment protocols, with iterative model updates planned as more prospective data accrues. Nonetheless, to our knowledge, the current study represents the first in the IMRT-era to identify a specific RPA-derived threshold dose-volume associated with ORN. As such we hope this work will spur future efforts to pool multisite ORN incidence and dosimetric data for bolstering of our evidentiary certainty for risk stratification and dose prescription.

While ORN rates may not be as high as in the 3DCRT era, mandibular sparing should be, whenever feasible but without compromising target coverage, aggressively pursued with IMRT. It also remains to be seen what the alteration in head and neck cancer demographics will bring in terms of ORN rates. Patients with human papillomavirus (HPV) related oropharyngeal carcinoma are a demographically growing portion of domestic cases. These patients often present with level II lymphadenopathy at comparatively higher rates than laryngeal cancer, necessitating greater mandibular coverage due to adjacent nodes in many cases.

Furthermore, patients with HPV-related oropharyngeal carcinoma are comparatively more curable, and may have decades of risk for post-radiotherapy sequelae, such as ORN, to develop. Efforts to understand the natural history and pathophysiology of both ORN and subclinical mandibular injury are warranted. Our group has recently presented efforts in this direction by utilizing dynamic contrast-enhanced (DCE) MRI to detect acute radiotherapy-induced alterations in mandibular microvasculature[32]. This study demonstrated DCE-MRI can detect dose-dependent alterations in mandibular bone vascularity during IMRT, thus providing usable biomarkers of acute mandibular vascular injury and recovery temporal kinetics[32].

Finally, our data emphasize the need for more granular dose-response analyses. In a programmatic effort to define normal tissue[18, 33–35] and tumor response [36] profiles that include gradient-dose representation, future efforts are focused on determining not only DVH-based (2D) volumetric representations of dose, but include developing efforts at 3D-dose deposition differentials across mandibular sub-volumes using validated image-registration platforms[37]. Likewise, while this dataset, in contrast to previously presented salivary gland patient series[38], focused exclusively on oropharyngeal cancer patients in order to isolate a comparatively uniform treatment paradigm (e.g., avoiding cases with therapeutic oral cavity surgery as a confounder); future efforts will be directed at construction of comprehensive dose response models, including more elaborate classifiers of potential risk strata.

In conclusion, IMRT DVH differentials between patients with and without ORN occurred primarily in the intermediate “bath” dose range of 35–73 Gy, with V44 and V58 as the most discriminatory parameters. Mandibular V44<42% and V58<25% represent reasonable DVH constraints for IMRT plan acceptability, when tumor coverage does not obviate their application.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Co-author specific contributions

All listed co-authors performed the following:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
2. Drafting the work or revising it critically for important intellectual content;

3. Final approval of the version to be published;
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Specific additional individual cooperative effort contributions to study/manuscript design/execution/interpretation, in addition to all criteria above are listed as follows:

- ASRM, VS-Manuscript writing, statistical analysis, direct oversight of all image registration/segmentation/dose extraction, clinical and dosimetric data workflows; direct oversight of trainee personnel (MM, HE, MKJ).
- JS, BH- Statistical analysis, guarantor(s) of statistical quality, case-matching.
- KH-Oropharynx program toxicity collection database oversight, clinical and toxicity data curation, conceptual feedback and support.
- NG-Electronic medical record screening, automated case identification, data extraction, informatics software support.
- ASG-Database construction, clinical/oncologic oropharynx database curation and oversight, conceptual feedback and support.
- MM-Dosimetric and clinical data collection.
- HE, MKJ-Clinical data curation, data transfer, supervised statistical analysis, graphic construction, supervision of DICOM-RT analytic workflows.
- XD, RZ-Responsible for dose calculation, plan comparison, and dosimetric data extraction and analyses.
- GBG, JL, JP, BMB, SJF, WHM, JL, MC, TH, RC, AG- Direct patient care provision, direct clinical data collection; interpretation and analytic support.
- ES-Direct oversight for multidisciplinary Oropharynx Program; data collection/resource allocation and infrastructure support.
- RW- Direct oversight for multidisciplinary Oropharynx Program; data collection/resource allocation and infrastructure support personnel provision, project integrity, manuscript content and editorial oversight, direct career mentorship (SYL)
- DIR- Direct oversight for multidisciplinary Oropharynx Program; data collection/resource allocation and infrastructure support personnel provision, project integrity, manuscript content and editorial oversight, direct career mentorship (CDF)
- CDF, SYL- Co-corresponding author(s); primary investigator(s); conceived, coordinated, and directed all study activities, responsible for data collection, project integrity, manuscript content and editorial oversight and correspondence; direct oversight of trainee personnel (ASRM).

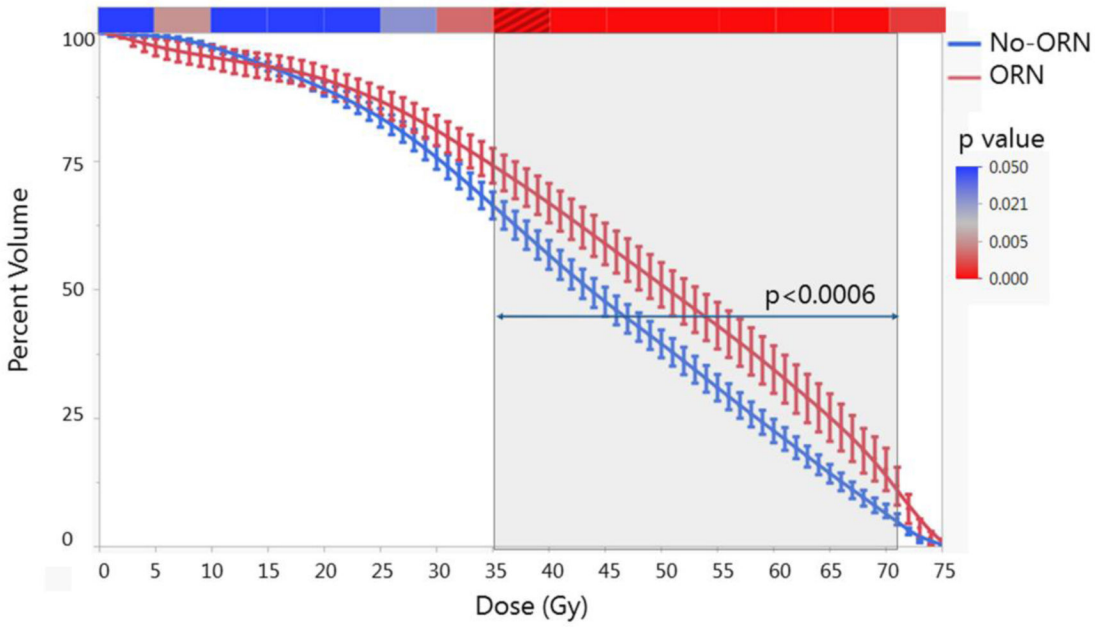

Figure 1.

Comparison of the Dose volume histograms (DVHs) between the plans for osteoradionecrosis (ORN) cases versus No-ORN controls; each error bar is constructed using a 95% confidence interval of the mean. P-value thresholding for multiple comparisons was used with $p < 0.0006$ considered significant for bins ranging from V35–V73.

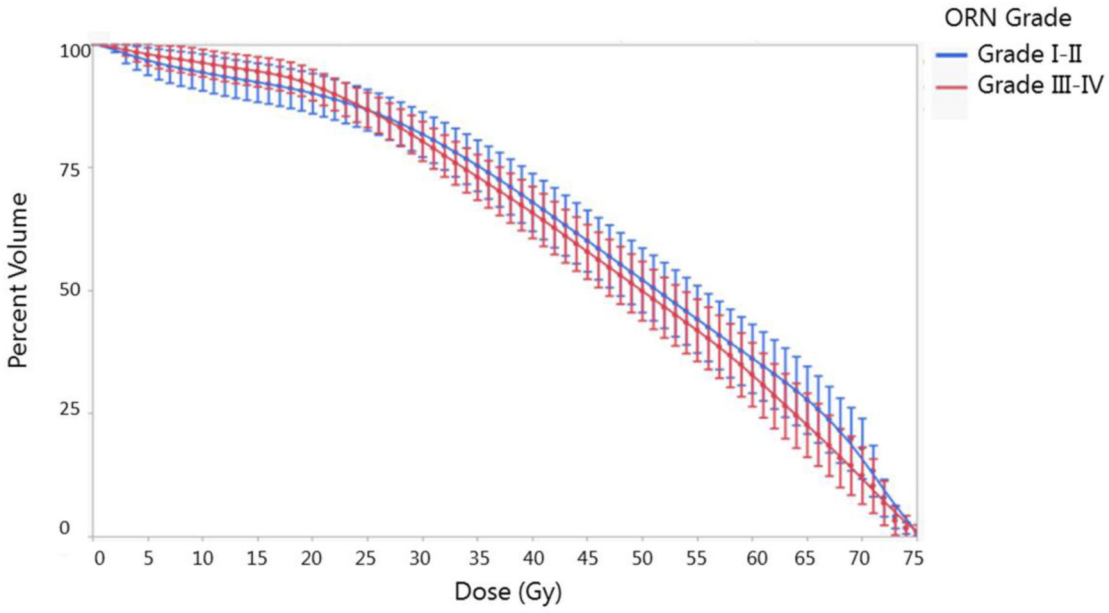

Figure 2.

Comparison of the Dose volume histograms (DVHs) between the plans for grades I–II osteoradionecrosis (ORN) cases versus grades II–IV; each error bar is constructed using a 95% confidence interval of the mean which overlaps across the entire range with no significant difference between both sub-cohorts.

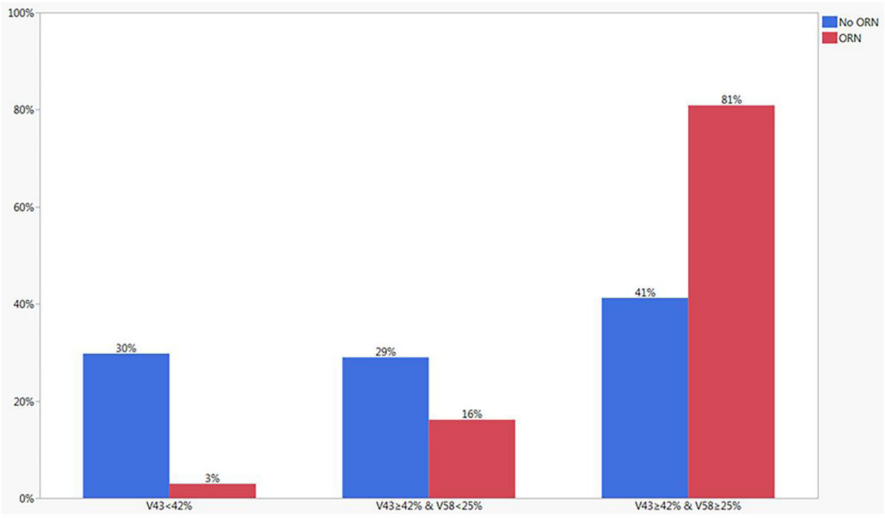

Figure 3.

Bar chart of osteoradionecrosis (ORN) rate in the entire dataset by various V43 and V58 combinations. The majority (81%) of ORN cases were observed in plans with both V44≥42% and V58≥25%.

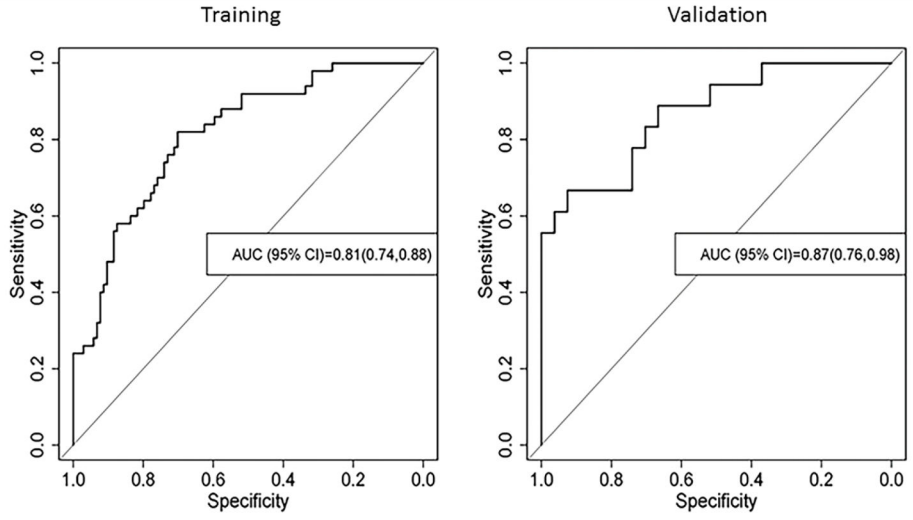

Figure 4.

Receiver operating characteristic (ROC) curve analysis showing discriminant capacity for the Bayesian quadratic discriminant analysis (BQDA) derived dose-volume parameters, with an observed area under the curve (AUC) of 0.81 (95% CI 0.74–0.88) for the training set and 0.87 (95% CI 0.76–098) for the 20% holdback validation set.

Table 1

Demographic, disease, and treatment characteristics of the matched case-control patients

Characteristic	ORN cohort (n=68) No. (%)	Control cohort (n=131) No. (%)	p-value
Age *			
median (range)	58 (36–75)	57 (36–77)	0.9
Sex *			
Male	61 (90)	117 (89)	
Female	7 (10)	14 (11)	0.9
Ethnicity *			
Caucasian	67 (99)	129 (98.5)	0.9
Others	1 (1)	2 (1.5)	
Smoking status *			
Never	26 (38)	52 (40)	
Former	21 (31)	42 (32)	0.9
Current	21 (31)	37 (28)	
Smoking pack-year			
Mean (SD)	30 (25.6)	29 (22)	0.9
Alcohol history			
Never	11 (16)	28 (22)	
Former	10 (16)	14 (11)	0.5
Current	47 (69)	83 (66)	
Disease subsite			
Base of Tongue	38 (56)	70 (53)	0.9
Tonsil	28 (41)	56 (43)	
Others	2 (3)	5 (4)	
T stage *			
T1	3 (4.5)	12 (9.1)	0.3
T2	28 (41)	58 (44.3)	
T3	20 (29.5)	41 (31.3)	
T4	17 (25)	20 (15.3)	
N stage			
N0	2 (3)	12 (9)	0.1
N1	1 (1.5)	6 (4.5)	
N2	63 (92.5)	105 (80)	
N3	2 (3)	8 (6)	
HPV status (p16 IHC)			
Positive	26 (38.2)	57 (43.5)	0.7
Negative	1 (1.5)	3 (2.3)	
Unknown	41 (60.3)	71 (54.2)	
Median Follow up			
Months (range)	60 (13–106)	66 (14–133)	0.1

Characteristic	ORN cohort (n=68) No. (%)	Control cohort (n=131) No. (%)	p-value
Dental status[^]			
No dental procedures	32 (47)	72 (55)	0.4
Dental extractions	35 (51.5)	55 (42)	
Edentulous	1 (1.5)	4 (3)	
Radiation Dose			
Mean in Gy (SD)	68.4 (4.0)	69.2 (2.0)	0.2
Radiation Fractions			
Mean (SD)	33.3 (4.3)	32.8 (2.4)	0.5
Therapy sequence			
Induction+RT	5 (7.35)	24 (18.3)	0.1
Concurrent CRT	41 (60.3)	68 (52)	
Induction+CRT	22 (32.35)	39 (29.7)	

[*] matching variables RT: radiotherapy; CRT: radiotherapy combined with systemic therapy,

[^] pre-IMRT dental status.

Table 2

Estimated means obtained from Bayesian quadratic discriminate model of the dose-volume parameters between Osteoradionecrosis (ORN) and non-ORN cohorts

Dose-volume parameter	ORN cohort (percent mandibular volume)	No-ORN cohort (percent mandibular volume)
V45	59.0	47.7
V49	52.6	41.2
V61	32.6	20.7
V65	25.2	13.9
V72	6.2	2.4